May 14, 2002

MEMORANDUM

SUBJECT: Transmittal of the Minutes of the Endocrine Disruptor Methods Validation Subcommittee under the National Advisory Council for Environmental Policy and Technology, held October 30-31, 2001

TO: Dorothy Bowers, Chair
National Advisory Council for Environmental Policy and Technology
Office of Cooperation and Environment Management
and
Peter G. Redmond, Designated Federal Official
National Advisory Council for Environmental Policy and Technology
Office of Cooperation and Environment Management

FROM: Jane Scott Smith, Designated Federal Official
NACEPT Endocrine Disruptor Methods Validation Subcommittee
Office of Science Coordination and Policy

THRU: Vanessa T. Vu, Ph.D. Chair
Endocrine Disruptor Methods Validation Subcommittee

Please find attached the final summary of the NACEPT Endocrine Disruptor Methods Validation Subcommittee open meeting held in Washington, D.C. from October 30-31, 2001. This meeting summary covers an overview of the Environmental Protection Agency=s Endocrine Disruptor Program, approached to test protocol validation and the scope, purpose and operating procedures of the endocrine Disruptor Methods Validation Subcommittee.

Information about NACEPT EDMVS meetings and activities can be obtained from the website at http://www.epa.gov/scipoly/oscpendo or the OPPT Docket Number OPPT 42212 at (202) 260-7099. Interested persons are invited to contact Jane Smith, EDMVS Designated Federal Official (DFO), via e-mail at smith jane-scott@epa.gov.

Attachment

cc:

Stephen Johnson
Susan Hazen
Adam Sharp
Dennis Deziel
Gordon Schisler
Sonia Altieri
OPPT Docket 42212D

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NOTICE

This meeting summary has been written as part of the activities of the National Advisory Council on Environmental Policy and Technology (NACEPT), Endocrine Disruptor Methods Validation Subcommittee (EDMVS). This meeting summary has not been reviewed for approval by the United States Environmental Protection Agency and, hence, the contents of the meeting summary do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use.

Congress amended the Federal Food Drug and Cosmetics Act (FFDCA) in the Food Quality Protection Act (FQPA) of 1996; it directed the U.S. Environmental Protection Agency (EPA) to develop a screening program to determine whether certain substances may have hormonal effects in humans. To ensure that EPA has the best and most up-to-date advice available regarding the validation of the Tier I and Tier II assays, the Endocrine Disruptor Screening Program, (EDSP), EPA recently established the EDMVS under NACEPT. The EDMSV provides independent advice and counsel to the Agency through NACEPT on scientific and technical issues related to validation of the EDSP Tier I and Tier II assays, including advice on methods for reducing animal use, refining procedures involving animals to make them less stressful, and replacing animals where scientifically appropriate.

The October 30-31, 2001 open meeting of the EDMVS was announced in the Federal Register on October 11, 2001 (Volume 66, Number 197). Further information about NACEPT EDMVS meetings and activities can be obtained from the website at http://www.epa.gov/scipoly/oscpendo or the OPPT Docket Number OPPT 42212 at (202) 260-7099. Interested persons are invited to contact Jane Smith, EDMVS Designated Federal Official (DFO), via e-mail at smith jane-scott@epa.gov.

EDMVS Members in Attendance for the October 2001 Meeting

William Benson, Ph.D., Vice Chair U.S. EPA	Gerald A. LeBlanc, Ph.D. North Carolina State University
Mildred Christian, Ph.D. Argus Research	Ron Miller, Ph.D. The Dow Chemical Company
Theodora Colborn, Ph.D. World Wildlife Fund	Susan C. Nagel, Ph.D. Duke University
Robert D. Combes, Ph.D. Fund for Replacement of Animals in Medical Experiments	James W. "Willie" Owens, Ph.D. The Procter & Gamble Company
Rodger D. Curren, Ph.D. Institute for In Vitro Sciences, Inc. (Participated by phone)	Thomas L. Potter, Ph.D. USDA-Agriculture Research Service
Peter L. deFur, Ph.D. Virginia Commonwealth University	Theodore H. Schettler, M.D., M.P.H. Science and Environ. Health Network
J. Charles Eldridge, Ph.D. Wake Forest Univ.School Medicine	Shane A. Snyder, Ph.D. Southern Nevada Water Authority
Penelope A. Fenner-Crisp, Ph.D. ILSI Risk Science Institute	James T. Stevens, Ph.D. Syngenta
David Hattan, Ph.D. Food and Drug Administration	William Stokes, D.V.M. NIEHS
Robert J. Kavlock, Ph.D. U.S. EPA	Glen Van Der Kraak, Ph.D. University of Guelph
William Kelce, Ph.D Pharmacia Corporation	Vanessa Vu, Ph.D., Chair U.S. EPA
Nancy K. Kim, Ph.D. NY State Department of Health	Valerie Wilson, Ph.D. Tulane/Xavier Center for Environ. Studies
Timothy Kubiak, Ph. D. U.S. Fish and Wildlife Service	James Yager, Jr., Ph.D. Johns Hopkins

Facilitator

Paul De Morgan
Resolve

Designated Federal Official

Jane Scott Smith
Office of Science Policy and Coordination

PRESENTERS

The Order of Their Presentations

Peter Redmond
EPA, OCEM, NACEPT, DFO

Gary Timm
EPA, OPPTS, OSCP

Elaine Francis, Ph.D.
EPA, ORD

Dave Hattan, Ph.D.
FDA, Division of Health

Jim Kariya
EPA, OSCP

J. Willie Owens, Ph.D.
Procter and Gamble

Jane Smith, DFO
EPA, OSCP

PUBLIC COMMENTS

Oral statements in the order presented

Mary Beth Sweetland
People for the Ethical Treatment of Animals

Jae Lee, MD
National Center for Policy Research for Women and Families

Angelina Duggan, Ph.D.
American Crop Protection Association

Sara Amundson
Doris Day Animal League

Nicole Cardello, M.D.
Physicians Committee for Responsible Medicine

Martin Stephens, M.D.
Humane Society of the United States

Rick Becker, Ph.D.
American Chemistry Council

Daniel Desaulnier, M.D.
Health Canada

Written statements were received from:

American Crop Protection Association
Humane Society of the United States

SUBCOMMITTEE RECOMMENDATIONS

The purpose of meeting was to present the mission of the EDMVS and discuss the roles and responsibilities of the subcommittee members. Due to the mature of the meeting, no recommendations and no interim recommendations were developer.

National Advisory Council for Environmental Policy and Technology (NACEPT)
Endocrine Disruptor Methods Validation Subcommittee (EDMVS)
First Plenary Meeting
October 30-31, 2001

Washington Dulles Airport Hilton
Grand Ballroom III
13869 Park Center Road
Herndon, VA 20171
703-478-2900

DRAFT Agenda

Meeting Objectives:

- Present overview of EPA=s Endocrine Disruptor Program.
- Provide background information on test protocol validation and approaches.
- Develop clear understanding of the EDMVS scope, purpose, and operating procedures.
- Determine next steps.

Tuesday, October 30, 2001

9:00 B 9:15 Welcome and Opening Comments
Dr. Vanessa Vu, Chair, Director, Office of Science Coordination and Policy, (OSCP), EPA
Dr. William Benson, Vice-Chair, Director, Gulf Ecology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, (ORD), EPA

9:15 B 9:45 Introductions and Agenda Review
Paul De Morgan, Facilitator, RESOLVE

9:45 B 10:00 Orientation to the Federal Advisory Committee Act and Ethics
Peter Redmond, Designated Federal Official, (DFO), of NACEPT, Office of Cooperative Environmental Management, (OCEM)

10:00 B 10:15 Overview of NACEPT
Peter Redmond, Designated Federal Official, (DFO), of NACEPT, Office of Cooperative Environmental Management, (OCEM)

10:15 B 10:30 Break

10:30 B 11:15 Overview of EPA=s Regulatory Program for Endocrine Disruptors
Gary Timm, OSCP, EPA

11:15 B 12:00 Overview of EPA=s Research Program for Endocrine Disruptors
Dr. Elaine Francis, ORD, EPA

12:00 B 1:00 Lunch

1:00 B 1:30 Overview of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Protocol Validation Process
Dr. Dave Hattan, FDA

1:30 B 2:15 Endocrine Disruptor Screening Program=s (EDSP) Approaches to Test Protocol Validation and Process: Relationships Between ICCVAM, Organization for Economic Co-operation and Development (OECD), EPA, and EDMVS
Gary Timm, OSCP, EPA

2:15 B 3:00 EDSP=s Test Protocol Validation Program: Status and Timeline
Jim Kariya, OSCP, EPA

3:00 B 3:15 Break

3:15 B 4:30 Illustration of OECD Test Protocol Validation Process: the Uterotrophic Assay
Dr. James W. Owens, Procter and Gamble

4:30 B 5:15 Public Comment
Members of the public will be given an opportunity to comment on any aspect of the EDMVS work. The amount of time given to each individual will depend on the number of people wishing to provide comment.

5:15 B 5:30 Setting the Stage for Day Two

<u>Wednesday, October 31, 2001</u>

9:00 B 9:45 Overview of the Mission Statement
Jane Smith, EDMVS DFO, OSCP, EPA

9:45 B 10:45 EDMVS Operating Procedures
Paul De Morgan, Facilitator, RESOLVE

10:45 B 11:00 Break

11:00 B 12:15 Looking Forward and Planning Next Steps

Identify information needs
Discuss agenda items and dates for next meeting(s)
Review action items

12:15 B 12:30 Summary of Meeting and Closing Comments

12:30 Adjourn

INTRODUCTION

The Office of Science Policy and Coordination's Endocrine Disruptor Screening Program, along with Governor Christie Whitman, Administrator, has completed the selection of members for the newly formed Endocrine Disruptor Methods Validation Subcommittee formed under the National Advisory Council for Environment Policy and Technology. The purpose of this meeting is to call the members together to review the mission statement and discuss their roles and responsibilities. Advance notice of the open meeting was published in the *Federal Register* on October 11, 2001 (Volume 66, Number 197). The meeting was held October 30-31, 2001 in Herndon, Virginia.

Endocrine Disruptor Methods Validation Subcommittee (EDMVS)
First Meeting
October 30-31, 2001

Meeting Summary/Minutes

On October 30-31, 2001, the U.S. Environmental Protection Agency (EPA) convened the first meeting of the EDMVS. The meeting had four objectives: 1) to present the overview of EPA=s Endocrine Disruptor Program; 2) to provide background information on test protocol validation and approaches; 3) to develop clear understanding of the EDMVS scope, purpose, and operating procedures; and 4) to determine next steps.

Monday, October 30, 2001

I. Welcome and Opening Comments

Dr. Vanessa Vu, EDMVS Chair and Director, Office of Science Coordination and Policy (OCSP), EPA opened the meeting. She thanked the subcommittee members for their time and commitment to environmental health issues. She gave an overview of the background of endocrine disruptor work at EPA over the past few years. As a result of heightened concern about endocrine disruptors, the Food Quality Protection Act and the Safe Drinking Water Act of 1996 including specific language directing EPA to develop a screening program for potential endocrine disruptors. EPA subsequently established the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), a diverse group of interests who worked for two years to develop a consensus set of recommendations around a screening and testing program for EPA to implement. EDMVS will be building off the EDSTAC work.

Dr. Vu also remarked that this and all EDMVS meetings are public meetings, noting the importance of participation and the value of issues brought to the table by the public.

Dr. Bill Benson, EDMVS Vice-Chair, and Director, Gulf Ecology Division, Office of Research and Development (ORD) at EPA, also welcomed the subcommittee and thanked members for their participation. He mentioned the aggressive timeline and workload of EDMVS and indicated his intent for the process to be team-oriented and focused on problem solving.

II. Introductions and Agenda Review

Mr. Paul De Morgan, a Senior Mediator with RESOLVE and the meeting facilitator, introduced himself and then asked each EDMVS member to identify themselves, their organizations, and to then give others a sense of their involvement in the endocrine disruptor arena (see attachment A for a list of members). He suggested members take a little longer than is usually taken for introductions, as the group will be meeting many times over a long period and should begin getting to know one another. These were followed by introductions from the EPA and RESOLVE staff members.

Mr. De Morgan gave an overview of the meeting objectives, agenda, and other materials distributed to the members. He also described RESOLVE=s multi-faceted role, which includes meeting facilitation to keep members on point and actively involved in discussions, mediation of specific issues as necessary, and assistance with meeting logistics. Finally, he outlined the ground rules that will apply at each meeting.

III Overview Presentations by EPA

A. Orientation to the Federal Advisory Committee Act and Ethics; Overview of NACEPT - Peter Redmond, NACEPT Designated Federal Official (DFO), Office of Cooperative Environmental Management (OCEM), EPA

Mr. Redmond reviewed the Federal Advisory Committee Act (FACA) of 1972 and its goals of promoting dialogue and developing consensus around public policy. He explained that all federal advisory committees have certain characteristics, including being transparent to the public and balanced with regard to different interests. He noted that EDMVS is not a technical advisory group, but rather a representative subcommittee of different views and expertise. He also pointed out the limits of federal advisory committees; specifically, after members provide their recommendations, it is the responsibility of the governing agency to exercise their decision-making and implementation authority.

Mr. Redmond then described the National Advisory Council for Environmental Policy and Technology (NACEPT) and its relationship to the EDMVS, noting that EDMVS is one of NACEPT=s five subcommittees. He indicated that a NACEPT member must serve on each subcommittee and for the EDMVS Valerie Wilson serves as the NACEPT representative. Mr. Redmond stressed the importance of ethical considerations in forming the subcommittee. He mentioned that although 90 percent of ethics issues are up to EPA to handle, subcommittee members should also reflect on whether they have a conflict of interest. If any subcommittee members feel they could possibly have a conflict of interest, whether in a personal portfolio, work, or otherwise, they should speak with Ms. Jane Smith, the EDMVS DFO. Mr. Redmond concluded by indicating any recommendations emerging from the EDMVS will need to be sent to NACEPT for review prior to being formally sent to EPA. He added that OSCP and NACEPT have a formal agreement for the timing of such a review and while NACEPT may ask EDMVS to respond to

questions about the recommendations, they will not be revising recommendations when forwarding them to EPA.

B. Overview of EPA=s Regulatory Program on Endocrine Disruptors B Gary Timm, Office of Science Coordination and Policy (OSCP), EPA

Mr. Timm outlined EPA=s two-pronged approach to endocrine disruptors, which involves research coordinated with screening, testing, and risk management. Research is led by ORD, while screening, testing, and risk management is led by OPPTS and serves as the primary focus of the EDMVS. He then discussed EPA=s sense of how the endocrine disruptor regulatory program will evolve over the next four years.

Mr. Timm also referred to the evolution of endocrine disruptor work at EPA, which was initiated legislatively by the Food Quality Protection Act of 1996. Within the statutory requirements of this act was a deadline to develop a screening and testing program by August 1998. To this end, EDSTAC was formed and ultimately issued 71 recommendations. Along with highlights of these recommendations, Mr. Timm explained the refined scope of the current Endocrine Disruptor Screening Program as well as the chemicals that fall under EPA=s purview. He explained the strategy being used to identify endocrine disruptors, involving initial sorting, priority setting, screening (tier 1), and testing (tier 2). This framework was summarized in the ACurrent EDSP Schematic for Phase I@ flowchart in his presentation.

Mr. Timm noted that a problem EPA faces is the lack of effects data for priority setting. Specifically, he noted that while EDSTAC recommended using High Throughput Screening (HTPS) technology, EPA=s efforts thus far had not been successful and therefore they are exploring use of Quantitative Structure Activity Relationship (QSAR) models as a prioritization tool. He indicated EPA is exploring two approaches, one being developed by the Food and Drug Administration=s National Center for Toxicological Research and another being developed in Bulgaria. Priorities for pesticides will be set differently than those for commercial chemicals. EPA plans on conducting a pilot program with 25-50 potentially high estrogen, androgen or thyroid (EAT) hazard concern@ substances to develop criteria for evaluating existing information and sorting pesticides and chemicals.

Next, Mr. Timm laid out the desired characteristics for Tier I screening and the proposed screening battery of *in vitro* and *in vivo* screens. Mr. Timm followed with the purpose and characteristics of Tier II testing and the proposed species to be studied in tier 2 tests.

Mr. Timm explained the development of policies and procedures thus far and how EPA intends to use them in implementation of recommended policy. He pointed out that endocrine disruptors policy will be regulated under existing laws and risk management activities and will be defined under these as well.

Following his presentation, Mr. Timm answered questions from the subcommittee. In response to questions, Mr. Timm provided the following information:

The priority-setting database is on track, though the QSAR effort is behind schedule. Validation of the AR binding model has not yet started. While the staff is unable to wait to make all decisions until the database is complete, it has reflected and responded to questions raised at the June 2000 Priority Setting Workshop. To address the data needs, 200 randomly selected chemicals and 50 chemicals predicted to be positive by each model were chosen for estrogen receptor (ER) QSAR models and will be tested in an ER binding assay. The resultant data on 300 (200+50+50) chemicals will be used to validate each of the QSAR models. He added, the source for the AEffects@ component of the database comes from literature reviews.

Mr. Timm stated that he is less familiar with the QSAR model from tests previously completed in Japan but would like a dialogue on their approach. He did note that the Japanese approach is looking at different properties. He also noted the possible benefits of duplicative QSAR models adding that Japanese tests could serve to complement the QSAR models. He stated he was also aware that the Japanese were developing a QSAR using a docking model approach. EPA is interested in the data but has not committed to using it at this point.

Regarding the flowchart describing risk assessment and the role of EDMVS, Mr. Timm explained that the subcommittee has responsibilities in AAssay Development@ and AStandardization and Development/Validation". Though Tier II evaluations will not be completed until 2005, EDMVS will also have involvement in initial protocol and methods development for Tier II testing.

In response to a question regarding priority setting and assessment of pesticides, Mr. Timm explained that pesticide data would be reviewed for evidence of endocrine disruption as it is submitted for tolerance reassessment and reregistration. However, these are 10 and 15-year cycles respectively. Thus, to screen/test/assess pesticides in a reasonable time frame, EPA will look at pesticides that have recently been through these processes. One of the purposes of the pilot is to determine the best way to accomplish this goal.

Regarding non-pesticide chemicals, Mr. Timm noted the chief problem is a lack of information related to endocrine disruption potential. At the present time, QSARs and HTPS methods are most highly developed for estrogen binding so EPA tends to focus on those. Efforts to develop an androgen receptor (AR) binding QSAR have been hampered because people have not, until recently, found enough AR binders to form training set for a model.

Thus, the first group of chemicals may be selected with an inordinate reliance on ER binding as a mode of action.

C. Overview of EPA=s Research Program for Endocrine Disruptors B Dr. Elaine Francis, Office of Research and Development (ORD), EPA

Dr. Francis outlined the role of ORD, the research arm of EPA, indicating it has responsibility for high priority areas such as endocrine disruptors. She shared with EDMVS the work that has been completed to date, as well as the long-term goals and corresponding timelines of ORD=s multi-year plan. Dr. Francis also discussed the components of intramural and extramural research, as well as how research is being coordinated on an interagency and international level. She concluded her presentation with information on the results of current and future research and their implications in preventing exposure of humans and wildlife to endocrine disruptors.

Following her presentation, Dr. Francis responded to questions and comments from EDMVS,
providing the following information:

Research is not being conducted on sewage sludge, but waste water discharges are being studied.

ORD is working with the European Union=s Research Directorate, and, for the regulatory side of Endocrine Disruptor Screening Program (EDSP) issues, OSCP is collaborating with the EU.

While information regarding high-risk exposure groups is an immediate need, EPA will not have the results for seven years.

ORD is looking at environmental levels of endocrine disruptors irrespective of known or unknown effects. In constructing dose-response curves, much research has focused on mammals.

EPA=s expertise in epidemiology has increased in the past few years.

Agricultural research into endocrine disruptors differs from epidemiological studies in that they are treated as a series of pilots that have evolved over years. Work by the National Cancer Institute, NIEHS, and EPA has looked at exposure to farm families. Currently, there is work in progress for a solicitation to fund 11 or 12 scientists in academia to look at developmental and reproductive endpoints.

D. Overview of the Interagency Coordination Committee on the Validation of Alternative Methods (ICCVAM) Test Protocol Validation Process - Dr. David G. Hattan, Director, Division of Health, Food and Drug Administration

Dr. Hattan presented a timeline of events that led to the establishment of ICCVAM and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which provides technical and operational support to ICCVAM. He explained that the 1997 report of the ad hoc ICCVAM, *Validation and Regulatory Acceptance of Toxicological Test Methods*, provides criteria for validation and regulatory acceptance of test methods and also a process for regulatory acceptance of test methods.

Dr. Hattan stressed that there are two distinct prerequisites for using new methods: first is scientific validation, which includes a determination of the usefulness and limitations of a test method for a specific purpose and a determination of relevance and reliability; and second is acceptance for regulatory use, which includes a determination that the proposed use of data from the new method will provide for a comparable or better level of health or environmental protection than the current approach. Dr. Hattan outlined the criteria for test method validation and for test method acceptance presented in the ad hoc ICCVAM report. He explained the stages of the process for new testing methods validation process (research, test method development, prevalidation, validation, peer review, regulatory acceptance, and implementation) and briefly described the ICCVAM Test Method Submission Guidelines. Dr. Hattan finished his presentation by listing the ICCVAM working groups and the ICCVAM/NICEATM scientific peer review panels.

Discussion following the presentation included the following point:

Dr. Hattan explained that the validation process for the local lymph node assay (LLNA) took a long time, but the process has been improved since then. He commented that the LLNA process had included may tests and

had begun with little existing information. An EDMVS member added that the LLNA process had encountered problems with non-confounded and negative runs. Another member commented that generally the process takes about ten years from the start of test method assessments to agency acceptance.

E. Endocrine Disruptor Screening Program=s (EDSP) Approaches to Test Protocol Validation and Process: Relationships Between ICCVAM, Organization for Economic Co-operation and Development (OECD), EPA, and EDMVS B Gary Timm, OSCP, EPA

Mr. Timm summarized the statutory requirements for the EDSP. He also listed the program=s Aprocess realities,@ aspects of the program not explicitly required by statute, which include, among others, involving stakeholders throughout the process and following the ICCVAM process for validating test protocols. He explained that the generic steps of the ICCVAM process, which EPA will follow, are method development (including prevalidation and validation), scientific peer review, and regulatory acceptance and implementation.

Mr. Timm described the roles of OECD, ICCVAM, and EPA and then listed which of the three would serve as lead organization for validation of each of the assays. He explained the steps of the EPA process for domestic guidelines. He also summarized the OECD process for international guidelines, noting that OECD=s Endocrine Disruptor Testing and Assessment Workgroup will be the primary vehicle for deliberation under this process. He said that the U.S. will be the lead country on most of the guidelines undergoing the OECD process. He stressed that for any of the international guidelines, if OECD does not conduct peer review, EPA will.

Mr. Timm summarized the key concepts in the EPA validation approach, noting that for battery validation, EPA will analyze results across assays and choose those that are most effective and efficient as a whole. He then presented the general outlines of the documents that will be produced at each stage of the process for each test method: a detailed review paper, a prevalidation report, and a validation report, as well as a summary report presenting the critical information from the other three documents. He said that EPA=s contractor will do the laboratory work and prepare these reports, and EDMVS will do a critical review of the reports and the recommendations therein.

In response to questions, Mr. Timm made the following points:

Animal welfare considerations will be discussed both in the detailed review papers and in the validation reports.

Criteria for selecting independent peer reviewers include that they have had no involvement in development of the assay and have no financial interest in the assay. Reviewers will be considered Aspecial government employees,@ compensated by EPA and subject to the full list of ethical considerations.

Regardless of whether a method undergoes validation by EPA, ICCVAM, or OECD, it will have to undergo a review for regulatory acceptance by an agency.

The ICCVAM peer review process is more rigorous than the usual OECD process, which involves consideration of comments gathered and distilled by the national coordinators. The U.S. will push for a more rigorous peer review but OECD may not agree. OECD has promised to conduct an independent peer review of the uterotrophic assay, but has not committed to specific process details. A committee member suggested that the OECD peer review process is more peer >involvement= than >review.=

EDMVS members are welcome to bring forward new assays for EPA to consider validating. However, assays proposed by EPA for the EDMVS based on the EDSTAC recommendations would take priority and the new assays would most likely be in a >second generation= tier 1 screening battery.

F. EDSP=s Test Protocol Validation Program: Status and Timeline B Jim Kariya, OSCP, EPA

Mr. Kariya introduced the timeline for the validation program as stipulated in the settlement agreement with the Natural Resources Defense Council. He pointed out that EPA had met the first of the Settlement Agreement deadlines (for development of the architecture of the Priority-Setting Database), and announced that EPA believes it is unlikely to meet the next deadline, a Dec. 31, 2001 commitment to complete and validate the QSAR portion of the Priority-Setting Database.

Mr. Kariya added that even though the Priority-Setting Database is not part of the EDMVS charge,

he wanted to take advantage of the EDMVS meeting to make the announcement publicly. He then summarized the status of each of the tier 1 and tier 2 assays, noting that OECD has completed the detailed review paper, prevalidation, and validation for the uterotrophic assay and the detailed review paper and prevalidation for the Hershberger assay. He noted that work is underway for several of the tier 2 assays, but no steps in any of the processes have been completed. Mr. Kariya presented the planned timelines for completing validation of each of the assays. He commented that it is difficult to include the *in utero* through lactation assay in either Tier I or Tier II, but EPA is following the recommendation of the EDSTAC and including it in tier 1. Mr. Timm commented that the *in utero* through lactation assay really is in its own category. Mr. Kariya noted that in the detailed timelines, some dates are approximate and not all details have been listed for steps relatively far in the future.

Mr. Kariya listed the papers and data that EPA plans to have ready for EDMVS review at the December, March, and June meetings. He also posed several questions for the subcommittee=s comments at this meeting.

Discussion following the presentation included the following points:

A member commented that EDSTAC members had generally agreed that an in utero through lactation assay would be desirable if one could be developed to meet the tier 1 criteria. He commented that EDSTAC members intended for such an assay to replace other assays, not to be in addition to the other assays. Mr. Timm replied that at this stage, many assays are being assessed, but that does not mean they will all be included in the battery. He said that there is a theory of what each assay might address, and those theories need to be tested. He observed that the assessment may show that the in utero through lactation assay can serve multiple purposes.

G. RTI Animal Research Facility (ARF) Fire Updates B Dr. Wayne Spoo, RTI

Dr. Spoo from RTI, a laboratory EPA is planning to use to perform previdation tests,

reported that a fire in August burned one rack of fifteen cages and part of the wall behind them. Copies of this presentation may be obtained through the docket. He said it is believed that the fire was started intentionally. He reported that smoke from the fire was pulled throughout the building by the ventilation system but was diluted as it spread. He said testing indicated that bisphenol A (BPA) was the only chemical that spread at concentrations that may have had an effect. He explained that an analysis determined that the highest possible concentration of BPA that could have spread from the fire was 5 parts per million (ppm), though the air in most of the building reached BPA concentrations around only 1 part per billion. He added that the threshold level for effects for BPA is 75 ppm. He said that the facility has been thoroughly cleaned and repainted since the fire, all questionable feed has been disposed, and currently no BPA is being detected in the facility. He reported that the panel assembled to review the potential effects of the fire concluded that it did not effect the studies underway and will not have an effect on future studies. He said that the EPA studies contracted with RTI are the one-generation extension study, scheduled to begin November 14, and the male and female pubertal assays, scheduled to begin no earlier than the first week of January. He added that none of the animals that will be used in these studies were in the building during the fire.

Discussion following the presentation included the following points:

A member questioned how RTI had concluded that a BPA concentration of 5 ppm has no effect when some research has shown effects at very low doses. She offered to share the literature with RTI staff. Dr. Spoo said he would review the information, but their conclusion was based on research on rats that showed no systemic effect of BPA until the concentration reached 75 ppm. Another member suggested that the fire and its aftereffects could be used to study low-dose exposure.

Asked whether RTI could assure EPA that a similar incident will not happen again, Dr. Spoo described some of the facilities security measures: guards monitor the comings and goings of all staff and visitors, and the security codes have been changed on all the doors and fewer people are allowed to have keys to the doors. He said that a decision on personnel review policies had not yet been made. He commented that a private investigator interviewed all staff who were in the building during the fire. He added that he expects RTI will begin doing security checks on employees.

A member expressed surprise at hearing that the facility uses polycarbonate

cages. He requested that EPA verify that the cages will not have an effect on the study endpoints.

Several members expressed concern that RTI has not been able to determine who set the fire.

A member commented that the fire is not the critical issue for these assays. He said he is more concerned about evaluating the data of the studies and information on the protocol, such as the dose selection and the chemicals being used, before agreeing that the studies should go forward.

EDMVS members indicated that the fire should not necessarily preclude RTI from doing studies for the EDSP. However, members asked EPA to wait to begin any assays at the facility until they could review the full report on the fire and the security measures now in place.

H. Ullustration of OECD Test ProtocolValidation Process: theUterotrophic Assay B
Dr. James W. Owens, Procter & Gamble

Dr. Owens presented background information on the uterotrophic assay, beginning with its origins
in the early 1930s. He shared data and observations from the OECD research program, as well as
discussing the study design, outlining chemical selection, dose response, coded multichemical, and
the phytoestrogen dietary analysis. He concluded that protocols have been standardized and are
consistent with high potency reference estrogen as well as five low potency weak estrogen agonists.
He stressed that the results were achieved even with the diverse competency of participating labs.

Finally, Dr. Owens noted the steps remaining before the assay is approved, including the final
statistical analysis, peer review planning, and the OECD test guideline review and comment.

Following his presentation, Dr. Owens took questions and comments from the subcommittee, responding with the following information:

The group size for the study was six. Body weight-adjusted controls were determined based

on analysis from data sent to NIEHS, who then notified researchers where statistical significance was first achieved in the dose-response curve.

An executive decision was made by the mammalian Validation Management Group to base dose selection on literature rather than delay several months and have the added cost of range-finding studies. Due to diverse practices and non-standard protocols, dose selection relied on professional judgment based on information available on weak agonists. In the future, labs will have to make this determination on their own.

Some labs chose a single protocol, while a fair number completed two or more. Four labs did all four with at least one chemical. The CVs of each protocol within a lab are available to review. Additional value was perceived from not choosing >perfect= labs as they will not exist when running the assay as part of the EDSP.

IV. Public Comment

After the conclusion of presentations, members of the public attending the meeting were given the opportunity to provide comments. Mr. De Morgan indicated that each person=s comments would not be captured verbatim, but rather just briefly summarized, and encouraged all to submit their comments in writing to Ms. Smith for inclusion in the EPA docket.

A. Mary Beth Sweetland, People for the Ethical Treatment of Animals

Ms. Sweetland mentioned the 1966 SOLNA criteria which were essentially used by ICCVAM and ECVAM. She cited her organization=s preference for using the ICCVAM process for validation of the Tier II and Tier II assays.

B. Jae Lee, MD, National Center for Policy Research for Women and Families

Mr. Lee encouraged EPA and EDMVS to keep in mind nonprofit and nonpartisan research organizations as a source of different perspectives on issues, if not technical assistance. He noted his organization=s interest in the association between endocrine disruptors and the onset of puberty in children.

C. Angelina Duggan, American Crop Protection Association

Dr. Duggan conveyed that her organization would like to provide recommendations for pilot programs and

urged that EPA continue to operate with an open and transparent process.

D. Sara Amundson, Doris Day Animal League

Ms. Amundson encouraged the continuation of interagency coordination in regards to funding, testing, and validation, describing the ICCVAM procedure as a way to streamline the regulatory process. She supported a delay on the second one-gen study until data from the first is available and questioned the panel=s expertise on running validation studies and screening processes. She also raised questions regarding the EDMVS relationship with NACEPT and which EDMVS recommendations, and in what format, are officially forwarded to EPA.

E. Nicole Cardello, Physicians Committee for Responsible Medicine

Dr. Cardello expressed concern that there is no mechanism for incorporating tests beyond those recommended by EDSTAC. She commented that EPA is only working on one non-animal test and that human exposure and epidemiological data is absent from the program.

F. Martin Stephens, Humane Society of the United States

Dr. Stephens highlighted concerns from the animal protection community, including the importance of transparency, inclusion of stakeholders with diverse views, incorporation of the three R=s, using an ICCVAM-like process with no double standards, and international coordination.

G. Rick Becker, American Chemistry Council

Dr. Becker urged EPA to stick to the charge given to the subcommittee and the necessity to make available the results of completed studies. He stressed the importance of EDMVS=s opportunity to review data and advise the Agency on the four steps of each method.

H. Daniel Desaulniers, Health Canada

Mr. Desaulniers requested EDMVS consider immature animals, adding that response can be dependent on litter size. He noted that it is a good idea to use animals from the same litter although that limits >n.= He added that responses can be different in subcutaneous doses and that consideration should be given to estrogenic effect or toxic response.

V. Setting the Stage for Day Two

Mr. De Morgan touched on the agenda for day two, referencing the EDMVS Mission Statement and Operating Procedures. He acknowledged the importance of discussing issues before the subcommittee at this meeting, but added the group should recognize this two-year process is only beginning and the important meeting goal is to begin laying the groundwork for the entire two years.

Tuesday, October 31, 2001

VI. Review of EDMVS Documents

A. Overview of the Mission Statement B Jane Smith, EDMVS DFO, OSCP, EPA

Ms. Smith introduced the Mission Statement, stating that while it took the basic format of the original document from the Administrator, it had been modified based on public comment and stakeholder concerns raised in the April 23, 2001 Organizational Meeting. She also noted that it had been modified in a couple of instances to address a lack of parallel structure in some of the language. She pointed out that the changes could be seen, redline/strikeout, in the 4/23/01rev version of the Mission Statement, and that the 10/30 version represented the document with the changes incorporated.

In response to questions about the Mission Statement, the following answers or clarifications were provided by the EPA staff:

External peer review (Section 2, Objectives) will be conducted by independent, expert scientists who have neither been previously involved in the research nor have a financial interest in the results of the study. Mr. Timm explained that the process takes the same basic approach as ICCVAM, though EPA does not generally request names for those interested in serving on the review board.

If external peer review is completed and the board has no complaint with the study methods or results, the process would be complete. If the peer reviewers have suggestions, EDMVS may examine these comments and revise the original proposal.

EDMVS can expect to review any tier 1 and tier 2 methods that EPA considers. EDMVS will have the opportunity to review methods and give advice rather than write protocols.

Ms. Smith acknowledged the concern that unnecessary assays could be conducted, stating that EPA does not assume each assay will go through to completion. Though the Mission Statement references data configuration following the validation step, it is possible that assays could fall out following the review of data from pre-validation.

There is only one case in which there is overlap between the pre-validation and validation step. Most overlap that exists would be that of the DRP and pre-validation steps.

Based on discussion of the 10/30 version, EPA will make the following considerations in further revising the Mission Statement:

Since initial work such as that on the uterotrophic and Hershberger protocols was begun prior to the formation of EDMVS, EPA will draft a context setting piece for the mission statement. A context paragraph would be useful in defining what role EDMVS will and will not be taking for which tests. A subcommittee member suggested that the document also refer to EDSTAC as the group responsible for the methods chosen for testing.

EPA is willing to have EDMVS complete an additional review of data following pre-validation, as

long as the entire battery is not delayed entering validation due to one or two assays held up in the pre-validation step.

A member encouraged EPA to address the different use of the terms screens, tests, and assays, Tier I Screen and Tier II Test to ensure consistency.

It was agreed that EPA would revise the document and provide a red-line strikeout version for review prior to the December meeting. Included in the next version will be a contextual paragraph. EPA will also consider the long-term work plan for the group and the outstanding issue of stepwise testing, or the existing overlap of DRP and pre-validation as well as pre-validation and validation.

B. EDMVS Operating Procedures B Paul De Morgan, Facilitator, RESOLVE

Mr. De Morgan described the Operating Procedures to the subcommittee, highlighting portions of the document including the section on decision-making. In addition, he noted that the purpose and objectives sections would mirror the changes made by EPA to the mission statement. He emphasized that these were intended to be the rules under which the group would work together over the next few years. In general, members felt the document adequately addressed the issues that might arise as they worked together. However, there were some comments and suggested changes.

Under the "Composition" section, the following clarifications were made by the EPA staff:

The number of members stated in the document will be changed from 24 to 26.

As outlined in the NACEPT ground-rules, alternates will not be officially named in the event that an EDMVS member cannot attend a meeting. However, members may send an individual, after notifying the DFO, to be seated in close proximity to the table and they will have an opportunity to offer their opinion before a consensus is reached. Further, EPA cannot cover the travel expenses of such a substitute.

For the purposes of EDMVS, a Acontractor@ is anyone providing a service to EPA other than a subcommittee member. In general, technical contractors include Battelle and RTI.

Under "Meeting Procedures," EPA staff responded to subcommittee questions and comments with the following information:

FACA requirements do not apply to workgroups. However, any document received by EDMVS via a workgroup would become part of the docket.

Regarding meeting summaries, Mr. De Morgan clarified procedure on the following points:

Meeting summaries will be submitted to EDMVS for review prior to the next meeting. RESOLVE will review any comments and, if editorial in nature, make the changes. If they are substantive in nature, RESOLVE will work with the members to try to address the issues. For substantive issues that cannot be resolved there will be time scheduled in the first part of each meeting agenda for discussion. The final sign-off on the summary will come from the chair.

If recommendations coming out of EDMVS are not based on full group consensus, those who do not join in the consensus can provide a minority report, which will be noted in a meeting summary.

Comments will not be attributed to individuals in meeting summaries, unless specifically requested by

those making the comments.

VII. Clarification of EDMVS Roles and Relationship to ICCVAM, OECD

A. Roles and Responsibilities of EPA, OECD, ICCVAM, and EDMVS B Gary Timm, OSCP

In following up on questions raised the first day, Mr. Timm presented a table showing which entity is responsible for each of the major steps in the validation process depending on whether EPA, OECD, or ICCVAM is designated as the lead organization for the assay (see attachment B). Mr. Timm explained that he placed a question mark in the peer review box for OECD because OECD is still deciding what its peer review process will be. He reiterated that if the process OECD chooses is not rigorous enough, EPA will conduct a peer review.

Mr. Timm explained that EPA will continue to explore options for ICCVAM involvement in EPA's peer review process. He said two options are being considered: 1) ICCVAM would recommend peer reviewers for the independent panel, or 2) ICCVAM would administer the peer review for EPA. He commented that two factors in determining ICCVAM's role are the amount of work ICCVAM can feasibly undertake and legal requirements for EPA's Science Advisory Board in the review process.

Discussion following the presentation included the following points:

An EDMVS member commented that consultation with the National Marine Fisheries Service (NMFS) and the U.S. Fish and Wildlife Service (USFWS) in regard to the Endangered Species Act is an important step that is not on the matrix. He recommended that EPA determine where that consultation would best fit in the process.

Ms. Smith clarified that NACEPT=s role is to review EDMVS reports and recommendations and transmit them formally to EPA. She commented that she and Mr. Redmond are still working on the details of how EDMVS and NACEPT will interact most efficiently to meet the EDSP timeline.

Dr. Vu clarified that the table shows only the major steps of the process; ICCVAM plays an advisory role throughout the ICCVAM process, and the EDMVS will play an advisory role throughout the EPA process. A member reminded everyone that the process of validation is new, and the organizations involved are learning as they go.

B. Discussion of EDMVS Work Plan

Building on an issue raised the day before, Mr. Timm indicated EPA was still trying to determine what role the EDMVS should play in regard to the OECD process. He suggested three options:

EDMVS receives and reviews the information on all of the OECD-managed assays and provides input on what comments EPA should submit to the U.S. national coordinator;

EDMVS receives information on the OECD-managed assays as updates but does not advise EPA on how to respond; or

EDMVS receives information on the OECD-managed assays and provides input to EPA on certain assays of particular interest, such as the mammalian assays.

Mr. Timm and Mr. Kariya then reviewed the status of the specific assays and asked the members what sort of involvement they would like the EDMVS to have in regard to work that has already been completed, work that is now underway, and work that is scheduled to begin soon.

Points raised during the discussion included:

Several members commented that it would be difficult to advise EPA on a test battery without having reviewed all of the assays being considered for the battery.

Members noted that OECD will administer the process for the wildlife assays, and the EDMVS members with wildlife expertise could offer valuable input on those studies.

One member acknowledged that reviewing the OECD studies will add a significant amount of work to an already heavy workload and suggested that a subgroup might form to review some of the OECD studies.

A member pointed out that no report is prepared on the validation of the assays under OECD, adding to the challenge of reviewing the validation.

After the discussion, members agreed that they would like the EDMVS to have a high level of involvement reviewing the OECD-managed validations as well as the EPA-managed validations. They also agreed they would like to review the summary reports on work that has already been completed under EPA and the information on work now underway. They asked EPA to provide information on work that is about to begin so that they can review and comment on it at the next EDMVS meeting. EPA agreed to draft a work plan to help determine how to best use the time and expertise of the EDMVS and allow for a high level of engagement on each assay. EPA also agreed to work with OECD to try to find a more effective and efficient way to mesh the various processes.

VIII. Next Steps

EPA will develop a draft work plan for the EDMVS to address the relationship of EDMVS with OECD and the role of EDMVS in reviewing work already underway or completed.

EPA will revise the mission statement based on comments from EDMVS members.

RESOLVE will revise the operating procedures to incorporate revisions to the

mission
statement and other changes as discussed.
RESOLVE will email members logistic information for the December meeting.
In preparation for the December meeting, EPA and RESOLVE will distribute documents and materials to members as they become available. RESOLVE will email members a list of what materials they should expect to receive and the dates they will be sent.

IX. Closing Comments

Dr. Vu thanked the members for their patience and hard work and said she looks forward to working with them over the next years. She also thanked the EPA and RESOLVE staff, the speakers, and the public for their contributions to the meeting.

Attachment

Flipchart: Roles and Responsibilities of EPA, OECD, ICCVAM, and EDMVS
Attachment

Roles and Responsibilities of EPA, OECD, ICCVAM, and EDMVS

Who Manages the Process What is Done **ICCVAM EPA OECD Manage lab work** EPA EPA EPA **Coordinate/manage process** NICEATM EPA EDTA Secretariat **Advisory** ICCVAM EDMVS EDTA **Produce documents** NICEATM EPA/Battelle* (EPA) Secretariat **Peer review** Independent panel Independent panel ? **Regulatory acceptance** SAP/SAB EPA SAP/SAB EPA SAP/SAB EPA OECD

* Battelle - Battelle Memorial Institute, a research laboratory

Acronyms used in this Table

EDMVS - Endocrine Disruptor Methods Validation Subcommittee

EDTA - Endocrine Disruptor Testing and Assessment - of OECD

EPA - Environmental Protection Agency

ICCVAM - Interagency Coordinating Committee on the Validation of Alternative Methods

NICEATM - National Toxicology Program (NTP) Interagency Center for the Evaluation of alternative Toxicological Methods

OECD - Organization for Economic Co-operation and Development

SAB/EPA - Science Advisory Board of the EPA

SAP/EPA - Science Advisory Panel of the EPA

MINUTES OF THE
ENDOCRINE DISRUPTOR METHODS VALIDATION SUBCOMMITTEE
ON
OCTOBER 30-31, 2001
AT
WASHINGTON DULLES AIRPORT
HERNDON, VIRGINIA

This meeting covered an overview of the Environmental Protection Agency's Endocrine Disruptor Program, approaches to test protocol validation and the scope, purpose and operating procedures of the Endocrine Disruptor Methods Validation Subcommittee.

/s/

Ms. Jane Scott Smith, DFO
Endocrine Disruptor Methods Validation
Subcommittee of the National Advisory
Council for Environmental Policy and
Technology
Date: 5/14/2002

/s/

Vanessa T. Vu, Ph.D., Chair
Endocrine Disruptor Methods Validation
Subcommittee of the National Advisory
Council for Environmental Policy and
Technology
Date: 5/14/2002